Subclinical carotid atherosclerosis and cognitive function


Carotid artery atherosclerosis is a major risk factor for stroke and subsequent cognitive impairment. Recent studies indicate that carotid atherosclerosis without clinical stroke may also be an independent risk factor for cognitive decline and dementia. Ultrasonography is an easily assessable and non-invasive method to measure different stages of the carotid artery atherosclerotic process and is widely used in clinical assessment as well as in epidemiological and clinical research. We give a brief review of studies that have investigated degrees of the subclinical atherosclerosis in the carotid arteries in relation to cognitive function and dementia, and we discuss several possible mechanisms that could explain the association between atherosclerosis and cognitive impairment.

Introduction

Cardiovascular risk factors are associated with cognitive decline and the two major subgroups of dementia, Alzheimer’s disease (AD), and vascular dementia (1, 2). Vascular dementia and AD are thought to be two separated entities that share some common risk factors (3), but some authors have challenged this view and proposed that the neurodegenerative process of late-onset sporadic AD may be triggered by vascular changes (4). Cerebrovascular lesions or hypoperfusion to the brain are thought to explain the association between vascular risk factors and vascular dementia, but the possible link to AD is less clear.

Carotid artery atherosclerosis is a major risk factor for stroke and subsequent cognitive impairment (5, 6). Recent studies indicate that carotid artery atherosclerosis is an independent risk factor of cognitive decline and dementia also in individuals without clinical stroke (7, 8). Ultrasound is an easily assessable and non-invasive method to measure different stages of the carotid artery atherosclerotic process. The carotid bifurcation and the proximal part of the internal carotid artery (ICA) are predilection sites for atherosclerotic plaques. Thickening of the carotid artery intima-media layer in this area is the first sign of atherosclerosis (5). The role of subclinical atherosclerosis in the relation to cognitive function can be studied by the use of ultrasound measurement of the carotid arteries.

Carotid IMT and cognitive function

The intima-media thickness (IMT) of the arterial vessel wall can be assessed with ultrasound of the carotid arteries (Fig. 1), but ultrasound cannot distinguish between the intima and media layer of the wall (5). Atherosclerosis is mainly an intimal process with deposition of cholesterol, inflammation, and cell infiltration. Atherosclerotic plaques usually occur at sites of non-laminar turbulent flow such as the carotid bifurcation and the ICA, and measurement of the artery intima-media layer in these areas are likely to represent early stages in the atherosclerotic process. However, a diffuse thickening of the carotid artery intima-media layer can also represent a hypertensive hypertrofic response of the medial smooth muscle cells related to changes in local shear stress and tensile stress to the vessel wall. In clinical and epidemiological studies, IMT has usually been measured in the near and the far wall of the distal part of the common carotid artery (CCA-IMT), the carotid bifurcation (Bulb-IMT), and the proximal internal carotid
artery (ICA-IMT). When IMT is measured in areas were plaques are less frequent, such as in the distal CCA, it is possible that IMT more closely reflects a hypertrophic process rather than atherosclerosis.

In a cohort from the Cardiovascular Health Study (CHS) of 5888 participants 65 years or older, cognitive decline was significantly greater in subjects with CCA-IMT >1.28 mm and in subjects with ICA-IMT >2.01 mm on the digit symbol substitution test. The cognitive decline was greater in the APO-E\(_{4}\)/C15\(_{4}\) allele carriers (9). In the Framingham Offspring study, a subgroup of 1971 participants who went through carotid ultrasound examination and were followed with cognitive testing and MRI of the brain 4 years later, higher ICA-IMT in clinically asymptomatic subjects was associated with significantly poorer performance on cognitive tests. MRI markers of silent cerebral infarcts or white matter hyperintensities could not explain this association (10). In a German study (INVADE) of 2693 participants with no cognitive impairment and a mean age of 67.7 years at baseline, 174 subject developed cognitive impairment during the 2-year follow-up and high CCA-IMT at baseline was an independent risk factor for cognitive decline (11). In the Tromso study, we followed 4371 stroke-free middle-aged participants for 7 years and found that mean IMT of the near and far wall of CCA and the far wall of the carotid bifurcation at baseline was independently associated with lower cognitive test scores (unpublished data). In the Atherosclerosis Risk in Communities Cohort (ARIC), the average of the IMT of the near and far wall of the carotid CCA, bifurcation and ICA was negatively associated with scores on the digit symbol substitution test in cross-sectional analyses (12), but not with cognitive decline over 6 years in a prospective study of 10,963 subjects (1). A recent report from the ARIC MRI Study with 14 years follow-up of 1130 subjects (mean age at baseline 59 years) found no association between mean carotid IMT and cognitive decline (13).

In the Rotterdam Study, 6647 elderly subjects (mean age 69 years at baseline) were followed for 9.0 years, and 678 subjects developed dementia (476 had AD, 78 vascular dementia and 52 a combination of the two) during follow-up. High CCA-IMT at baseline was associated with increased risk of AD but not with vascular dementia when adjusted for age and sex (14). In a prospective 5 years follow-up sub-study in the CHS, subjects with CCA-IMT >1.16 mm had a hasard ratio (HR) of 1.5 and ICA-IMT >1.75 mm had a HR of 1.7 of developing AD. Carotid stenosis (1–100%) did not increase the risk of dementia and AD in this study (8).

**Figure 1.** B-mode ultrasound image of the carotid arteries with no atherosclerosis at the carotid bifurcation. The intima-media thickness can be followed in the near and far wall of the common carotid artery and in the far wall of the carotid bifurcation and internal carotid artery.

**Carotid plaques and cognitive function**

Early intimal thickening progresses to formation of atherosclerotic plaques (Fig. 2). Criteria for definition of atherosclerotic plaque on ultrasound examination have varied in different studies (15). A visually localized protrusion of the vessel wall of more than 50% of the adjacent (normal) IMT is a widely used definition of a plaque and is also used in the Tromso study (16). Plaque occurrence, number of plaques, plaque thickness, plaque area, plaque volume, and plaque echogenicity are different measures that can be used to assess the amount of carotid atherosclerosis.

**Figure 2.** Carotid atherosclerosis with the presence of an echogenic plaque in the far wall of the carotid bifurcation.
In a cross-sectional analysis of 284 demented (207 with AD) and 1698 non-demented subjects in the Rotterdam study, presence of plaques (age-adjusted) and high CCA-IMT were significantly associated with occurrence of both vascular dementia and AD (17). In the prospective analysis in the Rotterdam study, no association was seen between increased number of plaques and the risk of dementia (14). However, in a competing risk analysis, a significant negative trend was found between increasing number of carotid plaques and dementia or mortality, whichever came first. This suggests that the increased mortality rate in subjects with carotid plaques have attenuated a possible association between number of plaques and dementia.

**Carotid stenosis and cognitive function**

Small plaques do not significantly affect the blood flow or blood velocity, but increasing plaque size or number leads to narrowing of the vessel lumen, stenosis, and increased risk of embolization and hypoperfusion. Most studies on neuropsychological performance in carotid stenosis are based on small case series of patients undergoing carotid endarterectomy, but a few population-based studies have been published. In the Tromsø study, we examined 189 stroke-free subjects with carotid stenosis and 201 controls and found that carotid stenosis were associated with poorer performance on cognitive tests even after adjustment for relevant confounders (sex, age, and length of education). These differences could not be explained by a higher rate of silent MRI lesions such as lacunar or cortical infarcts or white matter lesions (18). In the CHS cohort of 4006 subjects, the presence of high-grade stenosis (≥75%) of the left carotid artery was seen as a significant predictor of cognitive decline defined as an annual drop of more than one point on the Modified Mini Mental Status Examination (3MSE). Results were also significant in a subgroup of 1893 subjects with no evidence of infarction on brain MRI (7). In the Framingham Offspring study, a subgroup of 1971 participants went through carotid ultrasound examination and were followed with cognitive testing and MRI of the brain 4 years later. Carotid stenosis was associated with significant poorer performance on cognitive tests in clinically asymptomatic subjects, and MRI markers of silent cerebral infarcts or white matter hyperintensities could not explain this association (10). A recent review conclude that carotid stenosis appears to be an independent risk factor for cognitive impairment in individuals without stroke and that the main mechanism is through embolization or hypoperfusion of the brain (19).

Carotid endarterectomy (CEA) is not recommended in asymptomatic carotid stenosis, and the effect of carotid revascularization procedures in high-grade carotid stenosis on cognitive outcome is unclear (19, 20). One large study of 1659 patients with asymptomatic carotid stenosis found no difference in the mean MMSE scores between those receiving medical therapy and those undergoing CEA after 5 years follow-up (21). Conflicting results on cognitive outcome are even seen after CEA in symptomatic carotid stenosis (20, 22).

**Discussion**

A majority of prospective observational studies find an association between subclinical carotid intima-media thickening, plaques, and stenosis on the one hand, and cognitive impairment on the other. Two studies also found that baseline IMT was predictive of AD.

Several possible mechanisms can explain the inverse association between subclinical carotid atherosclerosis and cognitive function. Carotid atherosclerosis is also a major risk factor for both silent and clinically recognized ischemic strokes, with subsequent cognitive impairment. The presence of silent brain infarcts on MRI at baseline more than doubled the risk of dementia and AD after 3.6 years follow-up in the population-based Rotterdam Scan Study (23). Cerebral small vessel disease and MRI detectable white matter lesions have also been associated with an increased risk of cognitive decline (24). However, three large population-based studies that examined the relation between carotid stenosis and cognitive function found the same inverse relationship between carotid stenosis and cognitive function independently of lesions detected in brain MRI (7, 10, 18). This indicates that neuropsychological tests is more sensitive of minor vascular microembolisms than MRI or that the effect on cognitive function is mediated through another pathway. Cerebral hypoperfusion because of high-grade stenosis could result in worsening of cognitive function. Rather than being a direct cause of reduced cognitive function carotid atherosclerosis may act as a marker of intracerebral and generalized atherosclerosis and cerebral small vessel disease with microangiopathy and reduced cerebral perfusion as a result (25).

Increased risks of AD with increasing IMT have been found in the Rotterdam and the CHS studies. Carotid atherosclerosis, cerebrovascular disease, and AD are frequent coexisting conditions in the elderly, but these studies indicate a causal
relationship between vascular pathology and AD. Whether vascular risk factors enhance the AD pathophysiological process or just add to clinical severity or hasten the age of onset is not known. Two large autopsy studies found no association between cerebral vascular lesions and the two hallmarks of AD, amyloid plaques and neurofibrillary tangles in individuals with AD, indicating no causative but maybe an additive effect of vascular lesions on AD (26, 27). In autopsy studies evaluating the degree of intracranial atherosclerosis with AD pathology, two studies found a strong association (27, 28), whereas one study found no association (29). Possible causative pathophysiological mechanisms for the association are unclear. Thickening of the carotid intima-media layer and development of AD may be two independent pathological processes that share the same vascular risk factors, especially high blood pressure (3). However, adjustment for cardiovascular risk factor did not attenuate the association between high IMT and increased risk of AD (14). As carotid intima-media thickening, and not stenosis, were associated with AD, the pathological pathway could be mediated through minor cerebral vascular changes and microangiopathy rather than intracranial large vessel atherosclerosis and stenosis. Cerebral hypoxia could destabilize neurons and contribute to a neurodegenerative process characterized by formation of neurofibrillary tangles and amyloid plaques (4). The results from the Rotterdam study showing that carotid intima-media thickening was associated with increased risk of AD, but not with vascular dementia, support this hypothesis (14). On the other hand, in the CHS study, peripheral artery atherosclerosis measured as low ankle-arm index was significantly associated with increased risk of AD, suggesting that generalized atherosclerosis is a risk factor for AD and that multiple pathophysiological mechanisms may explain the association (8).

Although population studies indicate that cardiovascular risk factors and carotid atherosclerosis are independent risk factors for cognitive impairment in individuals without prior cerebrovascular disease, it is not known if interventions to reduce these risk factors could delay cognitive decline in this group. Randomized controlled trials on blood pressure and lipid lowering treatment in the prevention of dementia and cognitive impairment have so far been disappointing (30, 31).

**Conclusion**

Subclinical carotid atherosclerosis measured as intima-media thickening, carotid plaques, and stenosis is inversely associated with cognitive function in several prospective studies. Two large prospective studies found an increased risk of dementia and AD with carotid intima-media thickening. On the basis of these observational studies, one might speculate that prevention of carotid atherosclerosis could protect against cognitive decline, but properly designed intervention studies are needed to demonstrate whether prevention or treatment of carotid atherosclerosis could lower the risk of cognitive impairment in individuals without prior cerebrovascular disease.

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**Conflict of interest**

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**References**